✍ Diagnosis of Viral Hepatitis

- **Hepatitis A**:
  - ✓ IgM anti-HAV in the serum indicates an acute infection. IgM appears 3 weeks after exposure and becomes undetectable within 6 months.
  - ✓ IgG anti-HAV indicates protection and lifelong immunity against hepatitis A. IgG appears in the serum at approximately the same time IgM antiHAV develops
- **Hepatitis B**

> **Key Concepts** *Heptatis B is diagnosed when **HBsAg** is detectable in the serum.*

  - ✓ Anti-HBc to IgM: indicates active infection.
  - ✓ Anti-HBc to IgG: either chronic infection or possible immunity against HBV
  - ✓ HBeAg is detected in the blood indicating active viral replication
  - ✓ Measurement of HBV DNA is used to determine viral infectivity and quantify viral replication.
- **Hepatitis C**

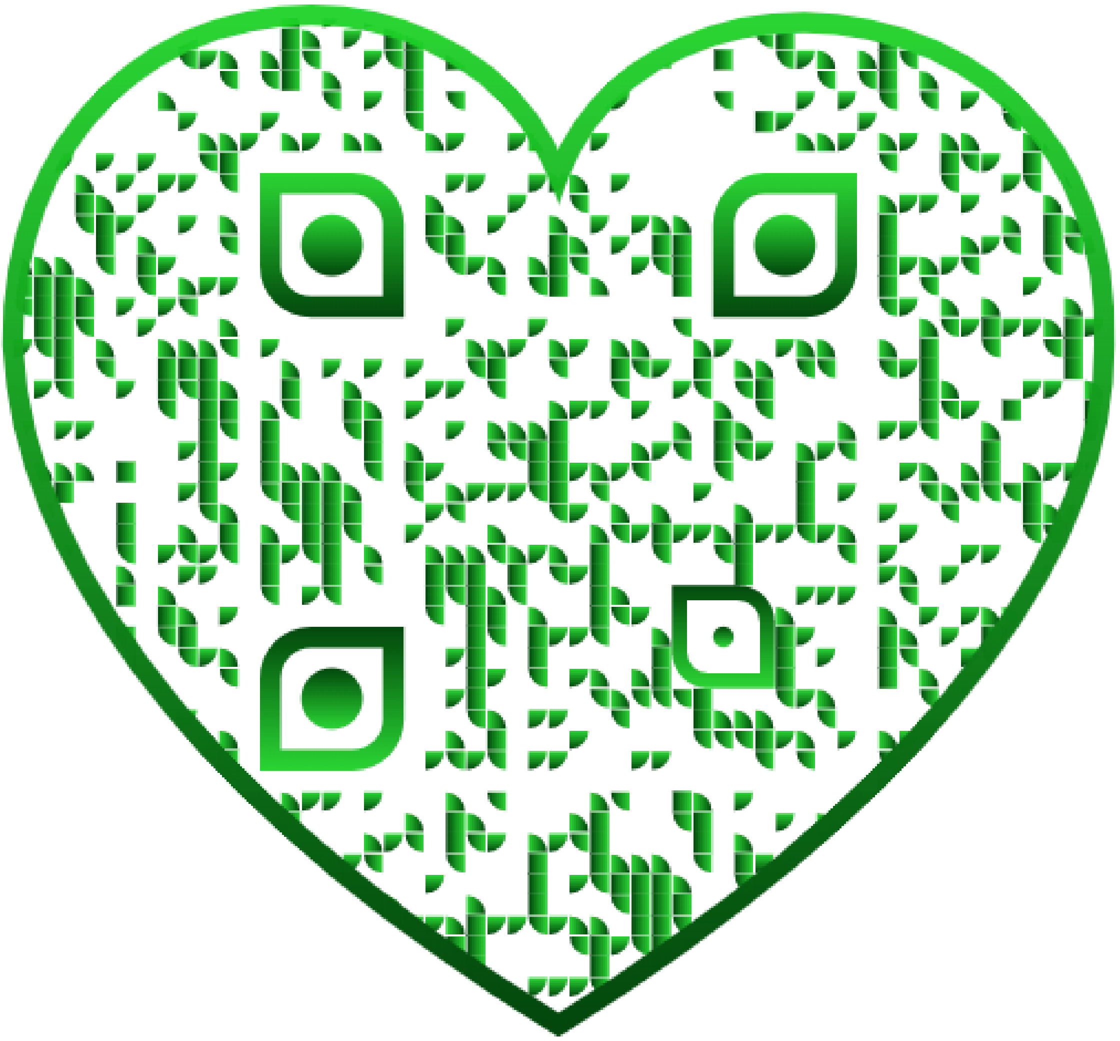
> **Key Concepts** *Heptatis C is diagnosed by testing for **anti-HCV** in the serum and confirmed by the presence of HCV RNA*

  - ✓ HCV RNA levels quantify viral replication and are used to determine if antiviral treatment for HCV is effective.
  - ✓ Once an infection has been confirmed, an **HCV genotype** should be obtained to determine the likelihood of response to antiviral therapy and the duration of treatment required
- **Hepatitis D**
  - ✓ Hepatitis D infection requires the presence of HBV for HDV viral replication.
  - ✓ Measuring HDV RNA levels in the serum PCR confirms the presence of the HDV
  - ✓ The presence of **IgM anti-HD** indicates active disease, and **IgG anti-HD** also becomes detectable if the infection does not resolve spontaneously.
- **Hepatitis E**
  - ✓ The diagnosis of hepatitis E is based on the presence of anti HEV antibodies (IgM anti-HEV).
  - ✓ IgG anti-HEV emerges when the acute phase of the HEV infection resolves

✍ Prevention

I) Hepatitis A Prevention

✓ Good personal hygiene and proper disposal of sanitary waste are required to prevent fecal-oral transmission of HAV. Individuals at high risk of acquiring HAV should receive either **serum immune globulin** or **HAV vaccine.**



2) Hepatitis B Prevention

- ✓ **Hepatitis B vaccine (Engerix-B, Recombivax HB)** is an inactivated virus administered intramuscularly in multiple doses. Hepatitis B vaccine is indicated for children and adults with occupational exposure to HBV, household and sexual contact of HBV carriers, men who have sex with men, people with multiple heterosexual partners, partners of patients with a newly acquired sexually transmitted disease, patients diagnosed with HIV, intravenous drug users, infants born to mothers with HBV, patients on hemodialysis, and patients with chronic liver disease.

Table 2.6 Dosing Regimens for Hepatitis B Vaccines

Product	Patient category	Dose (mcg)	Volume (mL)	No. of Doses	Schedule (months)
Recombivax HB	0 – 19	5	0.5	3	0, 1, 6
	≥20	10	1	3	0, 1, 6
Engerix-B	0 -19	10	0.5	3	0, 1, 6
	≥20	20	1	3	0, 1, 6

- ✓ **Mother – to -child transmission**

> **Key Concepts** *For **postexposure prophylaxis for perinatal exposure,** if the mother is **HBsAg positive**, newborns should be immunized within 12 to 24 hours after birth with the hepatitis B vaccine and HBIG 0.5 mL. If the mother is **HBsAg negative**, the newborn should receive only the hepatitis B vaccine.*

- ✓ **Hepatitis B Immune Globulin (HBIG):** Containing antibodies prepared from pooled human plasma that has a high concentration of anti-HBs. It provides passive immunization for postexposure prophylaxis against HBV. A single dose of HBIG 0.06 mL/kg IM is effective in preventing chronic hepatitis B infections in adults within 24 hours of exposure

Treatment

- ✓ HAV treatment is supportive or preventative in nature. Management of chronic forms of hepatitis consists of viral suppression (HBV) and virus eradication (HCV) to prevent long-term complications (eg, cirrhosis and hepatocellular carcinoma). Surrogate endpoints indicating treatment response include normalization of serum liver function tests (eg, ALT), reduced viral load, and histologic improvement. Treatment initiation for HBC and HCV is based upon viral load, liver histology from biopsy, and liver function tests.

1) Chronic Hepatitis B

- ✓ Not all chronic HBV patients are candidates for treatment.

- ✓ According to the American Association for the Study of Liver Diseases (AASLD)[1], the criteria for chronic HBV treatment is
  1) Anyone with HBeAg (+) or HBeAg (-) active HBV defined as: HBV DNA >2,000 IU/mL and ALT 2 x ULN and/or with evidence of histological disease
  2) Anyone with compensated or decompensated cirrhosis with HBV DNA >2,000 IU/mL
  3) Anyone not fulfilling above criteria with ALT < 2 × ULN and any detectable HBV DNA (<2,000 IU/mL), consider: patient's age, family history of HCC, prior history of HBV treatment and extrahepatic manifestations of HBV
- ✓ Chronic HBV can be treated with ***peginterferon alpha-2a*** or an NRTI.

Key Concepts ***Peginterferon alpha-2a*** *and the* ***NRTIs*** *are similar in efficacy for e-antigen positive and negative HBV; however, seroconversion of the e-antigen occurs more often at 1 year for peginterferon alpha-2a and 2 years for NRTIs. Viral resistance does not develop to peginterferon alpha-2a, but is associated with NRTIs.*

Lamivudine is plagued with a **high incidence of viral resistance and cross-resistance. Adefovir** is structurally similar to **tenofovir**, but is less potent than tenofovir in suppressing HBV levels. **Telbivudine** offers another option in select patients, but viral resistance was reported in 25% of patients after 2 years of treatment. When treatment with NRTIs is indicated, ***tenofovir*** and ***entecavir*** are preferred agents due to decreased chance of resistance, favorable side effect profile, and once daily dosing.

- ✓ There are two forms of tenofovir available: ***tenofovir disoproxil fumarate (TDF)*** and **tenofovir alafenamide.** TDF is available as a 300 mg dose for HBV. Tenofovir alafenamide is a **prodrug** converted to the active tenofovir in the hepatocyte, allowing for a lower dose at 25 mg. Tenofovir alafenamide offers several advantages over TDF as it allows more efficient delivery of tenofovir directly to the hepatocytes and thus a more direct action against HBV replication. In both HBeAg-positive and HBeAg-negative patients, tenofovir alafenamide was as effective as tenofovir DF and was more likely to result in normalization of ALT. The ability to reduce the systemic exposure to tenofovir allows for an improved safety profile. Compared to tenofovir DF, tenofovir alafenamide demonstrated improved bone safety and smaller changes in estimated glomerular filtration rates
- ✓ **Entecavir** has weak activity against HIV. If *it* is used in patients in whom lamivudine resistance is suspected, the higher dose of entecavir 1 mg/d should

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[1] Terrault NA, Lok AS, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS, Bzowej NH, Wong JB: **Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance.** *Hepatology* 2018, **67**(4):1560-1599.

be used. Studies involving combination therapy with NRTIs have not shown improved results compared to monotherapy; therefore, combination therapy is not warranted in most patients. Duration of treatment is:

(1) Pegylated interferon alpha-2a, for 48 wks
(2) NRTIs (lamivudine, adefovir, entecavir, telbivudine, tenofovir) for 6 – 12 months after HBsAg if HBeAg-positive patient or until loss of HBsAg if HBeAg-negative patient, usually indefinite

2) Chronic Hepatitis C

- ✓ Combination therapy of *interferon* and *oral ribavirin* improved sustained virologic response and the development of peginterferon allowed for weekly dosing and improved response over nonpegylated interferon.
- ✓ *Ribavirin* is a weak antiviral drug indicated for treatment of HCV when used in combination with *peginterferon alpha*.
- ✓ In recent years, the treatment of chronic HCV infection has changed considerably as various antiviral agents are approved. *Simprevir* is combined with peginterferon and ribavirin for genotype 1 with the total treatment duration ranging from 24 to 48 weeks, demonstrating SVR rates between 80% and 85%. *Sofosbuvir* was approved for genotypes 1, 2, 3, and 4. Sofosbuvir is combined with peginterferon and ribavirin for genotypes 1 and 4, but can be combined with ribavirin alone for genotypes 2 and 3. Sofosbuvir-based treatments have the highest SVR rates of all available HCV therapies.

Table 2.7 Treatment recommendations for HCV[1]

Genotype	SOF/DCV	SOF/LDV	SOF/RIB	PIFN/SOF/RIB
1a	12 weeks	8-12 weeks	Not recommended	12 weeks
1b	12 weeks	Not recommended	12 weeks	
2	12 weeks	Not recommended	12 weeks	12 weeks
3	12 weeks	Not recommended	24 weeks	12 weeks
4	12 weeks	12 weeks	Not recommended	12 weeks
5	12 weeks	12 weeks	Not recommended	12 weeks
6	12 weeks	12 weeks	Not recommended	12 weeks

- ✓ Note:
  - ↳ **SOF/DCV**: Sofosbuvir 400 mg oral once daily + Daclatasvir 60 mg oral once daily
  - ↳ **SOF/LDV**: Sofosbuvir 400 mg oral once daily + Ledipasvir 90 mg oral once daily
  - ↳ **PIFN/SOF/RIB**: Peglated Interferon 2a SC weekly + Sofosbuvir 400 mg oral once daily + Ribavirin 1000 mg (weight < 75kg), 1200 mg (weight ≥ 75Kg) daily in two divided doses.

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[1] Ministry of Health, Ethiopia. **National guidelines for prevention and control viral hepatitis in Ethiopia**, 2018, Addis Ababa

- **SOF/RIB:** Sofosbuvir 400 mg oral once daily + Ribavirin 1000 mg (weight < 75kg), 1200mg (weight ≥ 75Kg) daily in two divided doses

- ✓ Pregnant females with chronic HBV should be treated with an NRTI during the third trimester to prevent perinatal transmission.
- ✓ Peginterferon is pregnancy category C, but severe birth defects have occurred in fetuses exposed to ribavirin (pregnancy category X) either directly from the pregnant female or indirectly from the male sexual partner. All men and women of childbearing age should use two forms of contraception during ribavirin therapy and for 6 months following discontinuation of ribavirin.

Postexposure Prophylaxis

- ✓ Postexposure prophylaxis for HAV and HBV includes vaccination and immune globulin within 14 days of exposure to the virus. Immune globulin and hepatitis B immune globulin provide protection by imparting passive immunity for patients exposed to HAV and HBV, respectively.

> **Key Concepts** *For patients unvaccinated or with no history of recovery from HBV infection:* ***HBIG x 1 and initiate HB vaccine series****. For vaccinated patients with known history of recovery from HBV infection:* ***administer HB vaccine booster dose.***

2.4. Liver Cirrhosis and Complications

Definition:

- ***Cirrhosis*** is an advanced state of liver fibrosis and ***fibrosis*** is the replacement of injured tissue by scar tissue. Fibrosis is accompanied by a distortion of the hepatic vasculature leading to shunting of hepatic blood supply. The shunting compromises exchange between hepatic sinusoids and hepatocytes altering the functions of the liver.
- The consequences of cirrhosis include impaired hepatocyte function, portal hypertension, hepatocellular carcinoma, hepatorenal and hepatopulmonary syndrome, thrombocytopenia, and coagulopathies.
- Alcoholism and hepatitis C are the most common causes of cirrhosis.
- Medications associated with liver damage include amiodarone, statins, ART, ketoconazole, retinol, acetaminophen, anti-TB (R, H, Z), phenytoin, valproic acid, azathioprine and oral contraceptives.

Treatment of Cirrhosis Complications

(1) Portal Hypertension and Esophageal Varices

- Fibrotic changes within the hepatic sinusoids during cirrhosis increases the pressure gradient between portal and central venous pressures. The pressure gradient results in *gastrointestinal* and *esophageal varices*.
- Varices occur because the body attempts to find outlets to relieve the pressure of portal hypertension.

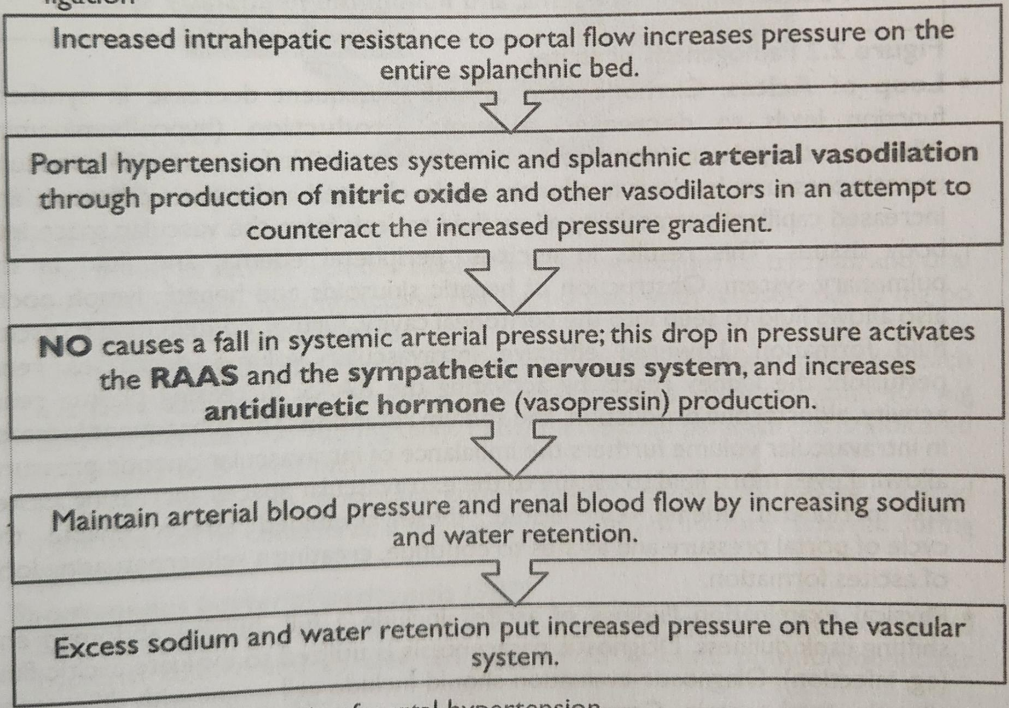
- The management of varices involves three strategies:

i) *Primary prophylaxis* (prevention of the first bleeding episode): propranolol

Key Concepts *The mainstay of primary prophylaxis is the use of nonselective β-adrenergic blocking agents such as* ***propranolol, nadolol****, or* ***carvedilol****. These agents reduce portal pressure by reducing portal venous inflow via two mechanisms: a decrease in cardiac output through β1-adrenergic blockade and a decrease in splanchnic blood flow through β2-adrenergic blockade that results in unopposed α-1 activity.*

ii) *Treatment of acute variceal hemorrhage*: antibiotic (norfloxacin /ceftriaxone) plus Octreotide plus variceal ligation

iii) *Secondary prophylaxis* (prevention of re-bleeding): propranolol plus variceal ligation



Increased intrahepatic resistance to portal flow increases pressure on the entire splanchnic bed.

Portal hypertension mediates systemic and splanchnic **arterial vasodilation** through production of **nitric oxide** and other vasodilators in an attempt to counteract the increased pressure gradient.

NO causes a fall in systemic arterial pressure; this drop in pressure activates the **RAAS** and the **sympathetic nervous system**, and increases **antidiuretic hormone** (vasopressin) production.

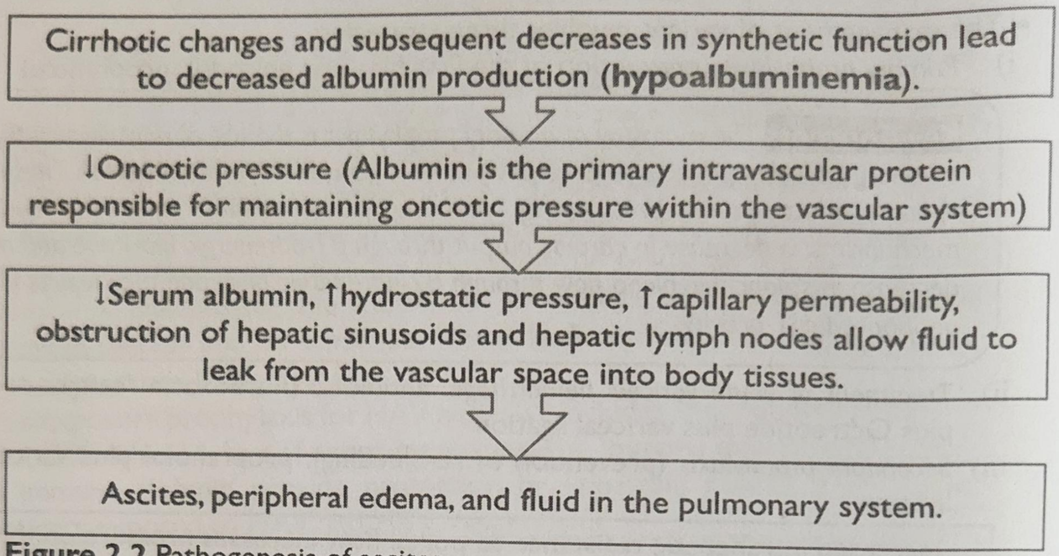
Maintain arterial blood pressure and renal blood flow by increasing sodium and water retention.

Excess sodium and water retention put increased pressure on the vascular system.

Figure 2.1 Pathogenesis of portal hypertension

(2) Ascites and Spontaneous Bacterial Peritonitis

- ***Ascites*** is the development of fluid retention in the setting of cirrhosis. *Ascites* is the accumulation of fluid in the peritoneal space.



Cirrhotic changes and subsequent decreases in synthetic function lead to decreased albumin production (**hypoalbuminemia**).

↓Oncotic pressure (Albumin is the primary intravascular protein responsible for maintaining oncotic pressure within the vascular system)

↓Serum albumin, ↑hydrostatic pressure, ↑capillary permeability, obstruction of hepatic sinusoids and hepatic lymph nodes allow fluid to leak from the vascular space into body tissues.

Ascites, peripheral edema, and fluid in the pulmonary system.

Figure 2.2 Pathogenesis of ascites

- **Loop of Acites**: Cirrhotic changes and subsequent decrease in synthetic function leads to **decreased albumin production** (hypoalbuminemia). Albumin is the primary intravascular protein responsible for maintaining vascular oncotic pressure; low serum albumin levels, elevated hydrostatic pressure, and increased capillary permeability allow fluid to leak from the vascular space into body tissues. This results in **ascites**, peripheral edema, and fluid in the pulmonary system. Obstruction of hepatic sinusoids and hepatic lymph nodes also allows fluid to seep into the peritoneal cavity, further contributing to ascitic fluid formation. Lowered effective intravascular volume decreases renal perfusion; the kidney reacts by activating the RAAS, increasing plasma renin activity, aldosterone production, and sodium retention. The subsequent increase in intravascular volume furthers the imbalance of intravascular oncotic pressure, allowing even more fluid to escape to the extravascular spaces, increasing ascites and peripheral edema. Unchecked, these combined effects enable the cycle of portal pressure and ascites to continue, creating a selfperpetuating loop of ascites formation.
- Physical examination findings of ascites include a full, bulging abdomen and shifting flank dullness. Diagnostic paracentesis is utilized to evaluate ascitic fluid (eg, infection). Diagnostic evaluation should include cell count with differential, albumin, total protein, Gram stain, and bacterial cultures. In patients without an established diagnosis of liver disease, the **serum ascites–albumin gradient** (SAAG) is used to determine the cause of portal hypertension: $\text{Alb}_{\text{serum}} - \text{Alb}_{\text{ascites}} = \text{SAAG}$, A value of **1.1 g/dL or greater** identifies portal hypertension as the cause of the ascites with 97% sensitivity. The differential diagnoses for SAAG values **less than 1.1 g/dL** (11 g/L) include peritoneal carcinoma, peritoneal

infection (tuberculosis, fungal, cytomegalovirus), and nephrotic syndrome. Serum albumin should be measured at the time of paracentesis for an accurate comparison

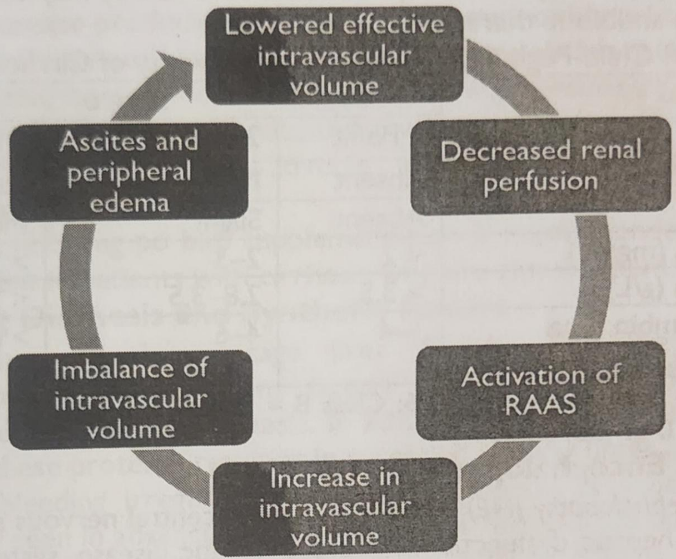

Lowered effective intravascular volume
Decreased renal perfusion
Activation of RAAS
Increase in intravascular volume
Imbalance of intravascular volume
Ascites and peripheral edema

Figure 2.3 Loop of ascites

- **Treatment**:

✓ Treatment of ascites includes alcohol avoidance, sodium restriction, and oral diuretic therapy. Spironolactone 100 mg po daily with furosemide 40 mg po daily maintains normokalemia.[1]

✓ Therapy can be titrated every 3-5 d (maintaining the 100:40 mg ratio) to reach adequate natriuresis and weight loss. Maximal doses: spironolactone 400 mg daily and furosemide 160 mg daily. Initial therapeutic paracentesis is indicated in patients with tense ascites.

✓ For resistant ascites, post-paracentesis albumin infusion of 6-8 g/L of fluid removed can be considered if large volumes (>5L) of fluid are removed during paracentesis.

- ***Spontaneous bacterial peritonitis (SBP)***

✓ SBP is an infection of ascitic fluid and is diagnosed by a positive ascitic fluid bacterial culture and an elevated ascitic fluid absolute polymorphonuclear count (> 250 cells/mm3).

✓ SBP is caused by E *coli*, K *pneumoniae*, and pneumococci.

✓ *Cefotaxime* 2 g IV every 8 h recommended in the community setting.

✓ Prevention of SBP: Long-term antibiotic therapy should be considered in high-risk patients (prior SBP, low protein ascites (< 1.5 g/dL), plus at least one of the following: serum creatinine ≥1.2 mg/dL, BUN ≥ 25 mg/dL, serum sodium ≤130 mEq/L, or Child-Pugh score ≥9 with bilirubin ≥3 mg/dL.Norfloxacin 400 mg po daily (or daily trimethoprim-sulfamethoxazole) may be considered for long term antibiotic therapy.

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[1] Runyon BA: **Management of adult patients with ascites due to cirrhosis: update 2012**. *AASLD Practice Guideline, AASLD* 2012, **3**(1):5-8.

Table 2.8 Child-Pugh Classification of the Severity of Cirrhosis

Variable	**Score**		
	1 Point	2 Points	3 Points
Encephalopathy	Absent	Mild-moderate	Severe to coma
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (g/L)	> 3.5	2.8–3.5	< 2.8
Prothrombin time (seconds above normal)	1–4	4–6	> 6

Class A = total score of 5 or 6; Class B = total score of 7 – 9, Class C = total score of 10 or more

(3) Hepatic Encephalopathy

- *Hepatic encephalopathy (HE)* is a disturbance in central nervous system function because of hepatic dysfunction. In severe hepatic disease, systemic circulation bypasses the liver; substances that are normally hepatically metabolized accumulate in the systemic circulation. These metabolic by-products, especially nitrogenous waste, are neurotoxic. **Ammonia** (NH_3) is just one of the toxins implicated in HE. It is a metabolic by-product of protein catabolism; it is also generated by bacteria in the GI tract. In a normally functioning liver, hepatocytes degrade ammonia to form urea, which is renally excreted. In cirrhosis, conversion to urea is reduced and ammonia accumulates, resulting in encephalopathy. Patients with HE commonly have elevated serum ammonia concentrations, but ammonia levels do not correlate with the degree of CNS impairment.
- Decreased cognition, confusion, and changes in behavior combined with physical signs such as asterixis (characteristic flapping of hands upon extension of arms with wrist flexion) indicate HE.
- The primary treatment for episodic and persistent HE is reducing ammonia blood concentrations.
- Ammonia levels are decreased by dietary restriction of protein, and drug therapy is aimed at inhibiting ammonia production or enhancing removal.
- **Treatment**

✓ ***Lactulose*** administration (oral or rectal enema) lowers ammonia blood levels by (1) creation of a laxative effect that reduces ammonia absorption, (2) leaching of ammonia into the colon and increasing bacterial uptake of ammonia, and (3) reducing ammonia production by interfering with the uptake of glutamine in the intestinal wall. In episodic HE, lactulose is initiated at a dose of 30 mL (20 g) orally every 1 to 2 hours until catharsis begins and the patient experiences one to two bowel movements. The dose is then adjusted to *produce two to three soft stools per day* for chronic therapy.

- ✓ Inhibiting urease-producing bacteria by using ***metronidazole*** (250 mg po bid) can also decrease production of ammonia. ***Neomycin*** has activity against most gram-negative bacteria and inhibits intestinal glutaminase thereby reducing bacterial production of glutamate and ammonia but it is rarely used due to the severity of its potential adverse effects including ototoxicity and nephrotoxicity.
- ✓ Oral **zinc** (220 mg po bid) supplementation is recommended for long-term management in patients with cirrhosis who are zinc deficient.

(4) Bleeding Diathesis and Synthetic Failure

- Coagulopathies signal end-stage liver disease. The liver manufactures procoagulant and anticoagulant factors essential for blood clotting and maintenance of blood homeostasis. In advanced disease, the liver is unable to synthesize these proteins, resulting in extended clotting times (eg, prothrombin time) and bleeding irregularities. Thrombocytopenia is another coagulation abnormality seen in advanced liver disease. This results from decreased platelet production in the bone marrow caused by reduced hepatic thrombopoietin synthesis and splenic sequestration of formed platelets. Macrocytic anemia occurs because of decreased intake, metabolism, and storage of folate and vitamin B12. Individuals who continue to drink alcohol exacerbate blood abnormalities because ethanol is toxic to bone marrow.
- **Treatment**: Vitamin K is essential for hepatic synthesis of coagulation factors. When given subcutaneously (10 mg for 3 days), Vitamin K1 (phytonadione) can replete stores and establish if coagulation abnormalities are due to decreased synthetic function alone. It is unusual to completely reverse clotting abnormalities. Because cirrhotic patients may have decreased bile production resulting in decreased absorption of fat-soluble vitamins, phytonadione should be given subcutaneously instead of orally to ensure absorption.

2.5. Inflammatory Bowel Disease (IBD)

✍ Definition

- IBD encompasses ulcerative colitis (UC) and Crohn disease (CD). Both disorders are associated with acute and chronic inflammation of the GI tract.
- Differences exist between UC and CD with regard to regions of the GI tract that affected and distribution and depth of intestinal inflammation.
- Patients with IBD may also develop inflammation involving organs other than the GI tract (extraintestinal manifestations).

✍ Epidemiology

- Inflammatory bowel disease is most prevalent in Western countries and in areas of northern latitude. A higher incidence of IBD occurs in the **Jewish** population, Black and Asian populations have a relatively lower incidence of IBD. Both sexes are affected somewhat equally with IBD

✍ Etiotogy

- The exact etiology of UC and CD is unknown; factors believed responsible for both conditions include infectious, genetic, environmental, and immunologic factors
- **Infectious factors**: Microorganisms are proposed to be a major factor in the initiation of inflammation in IBD. The presence of more **proinflammatory** bacteria in the GI tract, often referred to as dysbiosis. Patients with IBD have an **increased density** of intestinal microbiotica compared with those without IBD. The development and composition of the intestinal microbiotica may be influenced by **dietary factors**. The pathogenesis of IBD may involve a **loss of tolerance** toward normal GI bacterial flora.
- **Genetic factors:** studies of monozygotic twins demonstrate a high concordance rate of IBD in both individuals (particularly CD). First-degree relatives of patients with IBD may have up to a 20-fold increase in the risk of disease
- **Immunologic mechanisms:** the innate immune system largely involves the intestinal wall epithelial barrier and its associated secretions in response to contact with organisms. NOD proteins (for recognition of organisms) and toll-like membrane receptors (TLRs) are involved in intestinal **surveillance** and release of **antibacterial peptides** such as defensins. Reduction in defensin secretion is thought to be one contributing factor in the loss of effective barrier function. Consequently, the bowel wall in CD is infiltrated with lymphocytes, plasma cells, mast cells, macrophages, and neutrophils, often leading to formation of granulomas
- **Lifestyle, Dietary, and Drug-Related Causes:** intake of refined sugars has been associated with development of CD, while increased protein intake has been associated with a higher risk of developing IBD. Diet composition may directly influence the makeup of the gut microbiotica, possibly triggering IBD. The "hygiene hypothesis" proposes that cleaner conditions in more industrialized countries expose patients to fewer microorganisms at an early age. The immune response to these organisms is altered when encountered later in life. Diets low in fruits & vegetables and high in ω-6 polyunsaturated fats have been suggested to increase the risk of CD. Drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) that disrupt the integrity of the GI mucosa may facilitate mucosal entry of intestinal antigens and lead to IBD flares. Use of oral contraceptives has been associated with increased development of IBD in some cohort studies, but a strong causal relationship has not been proven. Smoking has protective effects in UC, leading to reductions in disease severity. In CD smoking may lead to increases in symptoms or worsening of the disease.

Pathophysiology

- UC and CD differ in two general respects: Extent and distribution of inflammation within the GI tract and depth of involvement within the bowel wall
- Ulcerative Colitis
  - ✓ UC is confined to the **rectum** and **colon**. It affects the mucosal and the submucosal layers. The deeper longitudinal muscular layers, serosa, and regional lymph nodes are not usually involved. Fistula, perforation, or obstruction is uncommon because this is a superficial inflammation. Complications of UC may be local, including hemorrhoids, anal fissures, or perirectal abscesses. Toxic megacolon: colonic distension of >6 cm, 7.9% of UC patients, death rates of up to 50%
- **Crohn's Disease**
  - ✓ CD is characterized as a transmural inflammatory process. The **terminal ileum** is most common site of the disorder, but it may occur in any part of the GI tract from mouth to anus. Ulcers are typically deep and elongated. It has "**cobblestone**" appearance of the bowel wall. Complications include bowel stricture and obstruction, fistula formation, nutritional deficiencies

Clinical Presentation

- Presenting symptoms common to both diseases include fever, abdominal pain, diarrhea (may be bloody, watery, or mucopurulent), rectal bleeding, and wt loss.

Table 2.9 Comparison of UC and CD

Clinical Findings	Ulcerative Colitis	Crohn Disease
Bowel involvement	Confined to rectum and colon Terminal ileal involvement (backwash ileitis) occurs in a minority of patients	May be anywhere from mouth to anus (66% of cases located in ileum)
Perianal involvement	Unlikely	Yes
Depth of ulceration	Superfcial	May extend to submucosa or deeper
Continuous inflammation	Very common	Rarely, a patchy, "cobblestone" appearance
Clinical Findings	Ulcerative Colitis	Crohn Disease
Histology	Nontransmural, crypt abscesses	Transmural lesions, Granulomas
Fistula, perforation, or strictures	No	Yes
Development of toxic megacolon	Yes	No
Malabsorption or malnutrition	Rare	Yes, vitamin deficiencies; possible growth retardation in children
Risk factor for colorectal cancer	Yes	Uncommon

Clinical Severity of UC

Mild	Moderate	Severe	Fulminant
✓≤ 4 stools/day (±blood) ✓No fever, anemia, or tachycardia ✓Normal ESR	✓4 stools/day (±blood ✓Minimal signs of systemic toxicity	✓> 6 stools/day with blood ✓Temp > 99.5°F HR > 90 beats/min ✓ESR > 30 mm/hr ✓Hb < 75% of normal ✓Abd tenderness ✓Bowel wall edema	✓> 10 stools/day with continuous blood ✓Temp > 99.5°F ✓HR > 90 beats/min ✓ESR > 30 mm/hr ✓Transfusions required ✓Abdominal pain ✓Dilated colon

Clinical severity of CD

1) **Mild-moderate**: Tolerates oral administration; absence of fever, dehydration, and abdominal tenderness; less than 10% weight loss
2) **Moderate-severe**: Failed treatment of mild-moderate; these symptoms usually present; possibly anemia, nausea and vomiting, considerable weight loss
3) **Severe-fulminant**: No response to outpatient steroids; high temperature, abdominal pain, persistent vomiting; possible obstruction, abscess, cachexia, rebound tenderness

Treatment

- Goals of therapy
  - ✓ Resolution of acute inflammatory processes,
  - ✓ Resolution of complications (e.g., fistulae and abscesses),
  - ✓ Alleviation of extraintestinal manifestations,
  - ✓ Maintenance of remission, or
  - ✓ Surgical palliation or cure.
- General management considerations
  - ✓ Rule out possible infectious causes of bloody diarrhea in patients with acute symptoms. Most patients will receive a colonoscopy to confirm the diagnosis and extent of disease.
  - ✓ *Surgery*: complications (abscess, fistula, perforation) occur or when fulminant disease is unresponsive to medical treatment
  - ✓ Most patients will require maintenance therapy because of the high incidence of relapse after induction therapy; the relapse rate is 35 – 80% at 2 years for CD and 50 – 70% at 1 year for UC
- **Adjunctive therapies:**
  - ✓ Loperamide: May be useful for proctitis or diarrhea; 2 mg after each loose stool (16 mg/day maximum)
  - ✓ Antispasmodics
    - ▪ Dicyclomine, 10–40 mg orally four times daily
    - ▪ Propantheline, 7.5–15 mg orally three times daily

- Hyoscyamine, 0.125–0.25 mg orally/slow release every 4 hours as needed

✓ Cholestyramine: Possibly for bile salt–induced diarrhea after ileal resection

- **Aminosalicylates**

✓ Used for both induction and maintenance of remission

✓ ***Sulfasalazine***: it is the prototype agent among the aminosalicylates. It is cleaved by colonic bacteria to the active (5-aminosalicylate) and the inactive carrier molecule sulfapyridine. Its efficacy is best in colonic disease (colonic activation of the drug). Adverse effects include GI disturbance, headache, arthralgia, folate malabsorption, rash, fever, pneumonitis, hepatotoxicity, bone marrow suppression, hemolytic anemia, pancreatitis, decreased sperm production. It should be avoided in patients with a sulfa allergy. Doses are 4–6 g/day for induction and 2–4 g/day for maintenance;

- ***5-Aminosalicylates*** (non – sulfa containing)

✓ These are better tolerated than sulfasalazine; considered first line in mild-moderate UC and CD. There are rare instances of nephrotoxicity with these products. Product selection depends on location of disease. ***Olsalazine*** is associated with secretory diarrhea in up to 25% of patients.

Table 2.10 5-Aminosalicylates for the management of IBD

Drug	Formulation	Daily dosage Range (g)	Site of action
Mesalamine	Enema	4	Rectum, terminal colon
	Delayed release capsule	1.6 – 4.8	Distal ileum, colon
	Suppository	1	Rectum
	Delayed-release tablet	2.4 – 4.8	Colon
Olsalazine	Capsule	1 – 3	Colon
Balsalazide	Capsule/tabs	2 – 6.75	Colon

- **Corticosteroids**

✓ Corticosteroids work quickly to suppress inflammation during acute flares. No role in maintenance therapy; however, more than 50% of patients with severe disease may become steroid-dependent. **Budesonide** is about 15 times more potent than prednisone; because of its high first-pass metabolism and limited systemic exposure, allow a 2-week overlap when changing from prednisone to budesonide to prevent adrenal insufficiency. Adverse effects (systemic therapy) are adrenal suppression, glucose intolerance, hypertension, sodium/water retention, osteoporosis, cataracts, and impaired wound healing.

Table 2.11 Corticosteroids for the management of IBD

Route	Agents	Dose	Comments
Oral	Prednisone Prednisolone	20–60 mg/day	Taper ASAP
	Budesonide capsule	9 mg/day PO; then 6 mg/day for up to 3 mo	Minimal absorption, minimal systemic adverse effects; indicated for treatment and maintenance of mild-moderate active CD involving terminal ileum or ascending colon
	Budesonide tablet	9 mg/day in the a.m. for 8 wk	
IV	Hydrocortisone Methylprednisolone	100 mg every 8 hr 15–48 mg/day	7- to 10-day course; change to PO when gut is functional

- **Immunosuppressives**

✓ Indicated only for maintenance because of long onset of action (3–15 months)

Table 2.12 Immunosuppresives for the management of IBD

Drug	Initial dose
Mercaptopurine	1-2.5mg/kg/day
Methotrexate	15-25mg/wk
Azathioprine	1-2.5mg/kg/day
Cyclosporine	2-4mg/kg/day

- **Biologic Agents**

✓ TNF-α inhibitors: Reduction in TNF-α activity is associated with improvement in the underlying inflammatory process. Examples of TNF-α inhibitors include: infliximab, adalimumab, golimumab, certolizumab

? REVIEW QUESTIONS

1. A 30-years old male patient was tested for viral hepatitis. His only past medical history is mild depression and diabetes. He has not had any surgeries. He is taking metformin and no other over-the counter drugs, or dietary supplements. All laboratory test results are normal except for the following: AST 93 IU/L, ALT 102 IU/L, HBsAg (+), HBeAg (-), Anti-HBc IgG (+), Anti-HBc IgM (-), Anti-HAV IgM (-), Anti-HAV IgG (+), Anti-HBe (-), Anti-HBs (-), Anti-HCV (-)
Which statement is **true** regarding this patient's viral hepatitis?
A. The patient has acute HBV infection
B. These test results indicate that active HBV replication
C. The patient is immune due to hepatitis B vaccination
D. The patient is chronically infected with HBV

2. A 24-year-old female medical student, presents to the emergency department after accidentally sticking herself with a contaminated needle while drawing blood from an HBsAg positive patient. She was not vaccinated previously. She weighs 56 kg. Which prophylactic treatment is appropriate for this woman?
   A. A single dose of HBIG as an IM injection within 24 hours.
   B. Hepatitis B vaccine at 0, 1 and 6 months and a single dose of HBIG within 24 hours
   C. Hepatitis B vaccine at 0, 1 and 6 months
   D. Administer 300mg tenofovir daily for 28 days
3. Which NSAID has the least risk of PUD than the others?
   A. Indomethacin B. Diclofenac C. Piroxicam D. Naproxen
4. **True** regarding gastric ulcer (GU) versus duodenal ulcer (DU)
   A. H. pylori infection commonly results GU whereas NSAIDs cause DU
   B. Pain from a GU is usually relieved by food intake
   C. Pain associated with DU occurs during the fasting state or at night
   D. Malignancy is more commonly found with DU than GU
5. Which of the following is **not** a common cause of peptic ulcer disease?
   A. Chronic alcohol ingestion B. NSAIDs
   C. Stress-related mucosal damage D. Helicobacter pylori infection
6. According to the American Society of Health-System Pharmacists (ASHP) guidelines, which of the following is **not** an indication for stress ulcer prophylaxis (SUP)?
   A. Mechanical ventilation for longer than 48 hours in the ICU
   B. A chronic heart failure patient attending the ambulatory setting
   C. Coagulopathy or hepatic failure patient in the ICU
   D. Hx of GI ulceration or bleeding within 1 yr of admission in the ICU
7. CT is a 30-year-old woman who will give birth to a baby boy in 2 months. Prior to becoming pregnant, she drank alcohol occasionally and did not smoke. She never used IV drugs or had a blood transfusion. The HBsAg test is positive. Which regimen should be recommended for her newborn baby?
   A. Hepatitis A vaccine at birth B. Hepatitis A and B vaccine
   C. HBIG within 24 hours of birth D. HBIG and hepatitis B vaccine
8. BM is a 43-year-old man brought in by emergency medical services for 'shortness of breath' and 'swelling.' Upon examination the patient is found to have tense, painful ascites. A therapeutic tap removes 9 L of ascitic fluid. Ascitic fluid from BM's paracentesis was sent to the lab for analysis. The results show SAAG 1.2 g/dL. How should these results be interpreted?
   A. SAAG of 1.1 g/dL or greater indicates peritoneal infection
   B. SAAG of 1.1 g/dL or greater indicates portal hypertension
   C. SAAG of 1.1 g/dL or greater indicates TB peritonitis
   D. SAAG of 1.7 g/dL or greater indicates a malignant source

9. A medical resident would like your recommendation for treating SBP, if present. Which one of the following recommendations would be most appropriate for BM?
   A. Cefixime 400 mg orally every 12 hours
   B. Moxifloxacin 200 mg orally every 24 hours
   C. Norfloxacin 400 mg orally every 12 hours
   D. Ceftriaxone 1 g IV every 24 hours
10. What is the most appropriate therapy to treat BM's ascites?
    A. Propranolol 10 mg orally twice daily
    B. Furosemide 20 mg IV every 6 hours and repeat paracentesis
    C. Spironolactone 100 mg and furosemide 40 mg orally
    D. Aldosterone 100 mg and furosemide 50 mg IV
11. Which of the following is the **correct** course of viral hepatitis progression?
    A. Jaundice → viral-specific antibodies → constitutional symptoms
    B. Constitutional symptoms → viral-specific antibodies → jaundice
    C. Increased serum ALT levels → jaundice → constitutional symptoms
    D. Ascites → jaundice → constitutional symptoms
12. Elderly patients with GERD can have the following defect in one of their protective host defense mechanisms:
    A. Decreased saliva production B. Increased bile acid production
    C. Increased GI motility D. Increased gastric emptying
13. In a patient with partial response to proton pump inhibitor therapy, which of the following are appropriate therapeutic strategies?
    A. Increase the once daily proton pump inhibitor to twice daily dosing
    B. Add famotidine 20 mg orally twice daily to the PPI regimen
    C. Switch to ranitidine 150 mg dosed once daily
    D. Switch to antacids and use as required
14. The preferred initial treatment option for a 45-year-old male presenting with a 3-month history of severe, continuous GERD symptoms is:
    A. Patient-directed therapy with OTC omeprazole
    B. Prescription strength H_2-receptor antagonist
    C. Prescription strength proton pump inhibitor
    D. Endoscopic therapy
15. Proton pump inhibitors exert their action by:
    A. Stimulating histamine-2 receptors in the gastric parietal cells
    B. Inhibiting gastric H+/K+-adenosine triphosphate in gastric parietal cells
    C. Inhibiting Na+/K+-adenosine biphosphate in the gastric parietal cells
    D. Inhibiting epithelial growth factor in the stomach
16. NSAID-induced ulcers differ from *H. pylori*-associated ulcers in that an NSAID-induced ulcer is:
    A. Most likely located in the stomach
    B. Most likely associated with less severe upper GI bleeding.

C. Most likely associated with a greater ulcer-related epigastric pain
D. Most likely associated with gastric acid hypersecretion

17. Which of the following best describes the presentation of patients with *H pylori*-induced ulcers?
A. Deep ulcer depth
B. A duodenal ulcer
C. Epigastric pain
D. Damage to the mucosa

18. A 30-year-old woman with a medical history of rheumatoid arthritis is *H pylori*-negative but undergoes endoscopy revealing a NSAID-induced ulcer. Assuming she has to continue the NSAID following a brief interruption, which is the preferred medication for ulcer healing and prevention of future ulcers?
A. Misoprostol
B. Omeprazole
C. Ranitidine
D. Sucralfate

19. A 43-year-old woman with no known drug allergies presents to the physician with a 2-week history of epigastric pain. She has no recent history of NSAID or antibiotic use. A serum antibody for *H pylori* is obtained and is positive. Which of the following would be considered the preferred initial therapy for *H pylori*?
A. PPI + metronidazole + levofloxacin
B. PPI + metronidazole + clarithromycin
C. PPI + amoxicillin + clarithromycin
D. PPI + metronidazole + bismuth + tetracycline

20. Which of the following is an endoscopic test used to diagnose *H pylori*?
A. Urea breath test
B. Mucosal biopsy
C. Fecal antigen
D. Antibody detection

21. A patient calls the pharmacy to complain about her tongue turning black after starting a new regimen for peptic ulcer disease (PUD). Which medication is causing the side effect?
A. Amoxicillin
B. Bismuth subsalicylate
C. Clarithromycin
D. Metronidazole

22. What is the recommended duration for initial treatment of *H pylori* using clarithromycin-based triple therapy?
A. 5 days
B. 7 days
C. 14 days
D. 21 days

23. Which diuretic regimen is preferred among a 64-year-old woman with marked abdominal distention and bulging flanks with dullness?
A. Amiloride
B. Eplerenone
C. Hydrochlorothiazide
D. Spironolactone plus furosemide

24. A 42-year-old gentleman was intolerant to lactulose for hepatic encephalopathy. What is an appropriate alternative agent for this patient based on the information above?
A. Ceftriaxone
B. Neomycin
C. Norfloxacin
D. Rifampicin

25. Which beta-blocker would be the preferred medication for a patient requiring primary prophylaxis for gastroesophageal varices?

A. Atenolol B. Bisoprolol C. Metoprolol D. Nadolol

26. The patient was successfully treated for an episode of spontaneous bacterial peritonitis (SBP). Which option is the most appropriate antibiotic as indefinite therapy for secondary prophylaxis of SBP?
A. Metronidazole B. Neomycin C. Norfloxacin D. Ceftriaxone

27. A 47-year-old woman with a history of alcoholic cirrhosis is admitted to the hospital and the team plans to initiate empiric therapy for spontaneous bacterial peritonitis. Which one of the following options is the best course of action at this time?
A. Albumin B. Cefotaxime
C. Vancomycin plus tobramycin D. Trimethoprim/sulfamethoxazole

28. A patient presents to the emergency department with moderate hepatic encephalopathy. In addition to supportive care, which medication would be first-line therapy to reduce nitrogenous load?
A. Lactulose B. Metronidazole C. Neomycin D. Vancomycin

29. Which of the following is a laboratory abnormality possibly indicative of cirrhosis?
A. Hyperalbuminemia B. Low alkaline phosphatase
C. Low prothrombin time D. Thrombocytopenia

30. A patient has completed one dose of the HBV vaccine. She is scheduled to receive her second dose of vaccine but the same brand of vaccine is not available. Which of the following is the BEST recommendation in this situation?
A. Continue her vaccine schedule with the available vaccine. Vaccines are interchangeable and require multiple doses for optimal effect.
B. Defer the vaccine until the same brand is available. Vaccines are not interchangeable.
C. Defer the vaccine until the same brand is available. HBV vaccine response is high with the first dose so she is likely already adequately protected.
D. Restart her vaccine schedule with the currently available vaccine

31. Which of the following agents is concerning for having a low-barrier to resistance?
A. Entecavir B. Lamivudine C. peg-IFN D. Tenofovir

32. All of the following HBV antivirals also have activity against HIV **except**:
A. Adefovir B. Emtricitabine C. Lamivudine D. Tenofovir

33. A 45-year-old man is found to be hepatitis C virus (HCV) antibody positive. Which of the following is the most correct interpretation of this result?
A. He is immune to HCV. B. He has active HCV.
C. He has either acute or chronic HCV D. He needs further evaluation

34. Which of the following is an appropriate treatment regimen for a noncirrhotic patient with HCV genotype (GT) 2?
A. Ledipasvir/sofosbuvir for 12 weeks

B. Ombitasvir/paritaprevir/ritonavir + dasabuvir for 12 weeks
C. Sofosbuvir and ribavirin for 12 weeks
D. Sofosbuvir and ribavirin for 16 weeks

35. In patients with Crohn's disease symptoms may be worsened by which of the following factors?
A. Use of acetaminophen B. High fiber diet
C. Tobacco use D. Exercise

36. Which of the following is more characteristic of Ulcerative Colitis disease than Crohn's Disease?
A. Confinement of disease to the colon and rectum
B. Fistula formation
C. Cobblestone pattern of inflammation
D. Deep inflammation of the intestinal mucosa

37. Which supplement may be required in patients receiving long-term therapy with sulfasalazine?
A. Zinc B. Folic acid C. Vitamin D D. Calcium

38. In patients with ulcerative colitis symptoms may be improved by which of the following factors?
A. Use of acetaminophen B. High fiber diet
C. Tobacco use D. Exercise

39. Which medication should be discontinued among a patient with cirrhosis and ascites?
A. Furosemide B. Lisinopril C. Naproxen D. Spironolactone

40. An appropriate nonpharmacologic recommendation for a pregnant patient with nausea and vomiting includes:
A. Eating large meals B. Eating two times a day
C. Using ginger D. Smelling trigger odors

41. A medical student recently heard about a new "hybrid" treatment regimen for H. *pylori* eradication and requests a literature search on this topic. Which of the following best represents a "hybrid" regimen?
A. Omeprazole, clarithromycin, and amoxicillin taken together for 14 days.
B. Ranitidine, bismuth, tetracycline, and metronidazole for 10 days.
C. Pantoprazole and amoxicillin taken together on days 1 to 5, followed by pantoprazole, clarithromycin, and metronidazole on days 6 to 10.
D. Rabeprazole and amoxicillin together for days 1 to 14, along with clarithromycin and metronidazole on days 7 to 14.

42. A 67-year-old woman with rheumatoid arthritis takes naproxen 500 mg by mouth daily, metoprolol 25 mg by mouth twice daily, aspirin 81 mg by mouth once daily, and alendronate 70 mcg by mouth weekly. Which is the best gastroprotective therapy to recommend?
A. Lansoprazole 30 mg daily.
B. Esomeprazole 40 mg twice daily.

C. Misoprostol 200 mcg twice daily.
D. No gastroprotective therapy necessary.

43. A 60-year-old woman has cirrhosis secondary to chronic hepatitis B infection hepatitis. Her medical history includes hypothyroidism and chronic back pain. She has new-onset abdominal pain and shortness of breath. She is afebrile with abdominal tenderness, including flank bulging and shifting dullness as well as a small pleural effusion. All laboratory values regarding electrolytes and renal function are within normal limits. She takes levothyroxine 75mcg once daily and oxycodone 10 mg every 8 hours as needed for pain. She has no drug allergies. Which is the best recommendation to treat her new-onset ascites?
A. Spironolactone 100 mg PO daily plus furosemide 40 mg by mouth daily.
B. Spironolactone 100 mg PO daily.
C. Spironolactone 40 mg PO daily plus furosemide 100 mg by mouth daily.
D. Furosemide 40 mg PO daily.

44. A 55-year-old man with HCV genotype 1b infection with HCV RNA of 4 million international units/mL who does not have cirrhosis and who is treatment naive is referred for treatment. He also has hypertension, depression, and stage 5 chronic kidney disease (receiving hemodialysis). His current medications include metoprolol 25 mg twice daily and citalopram 40 mg daily. Which combination would be most appropriate to prescribe for this patient's HCV treatment?
A. Glecaprevir/pibrentasvir x 8 weeks.
B. Ledipasvir/sofosbuvir x 12 weeks.
C. Sofosbuvir/velpatasvir/voxilaprevir x 12 weeks.
D. Sofosbuvir/velpatasvir x 8 weeks.

Questions 45 and 46 pertain to the following case.

A 45-year-old woman presents with sharp epigastric pain that is worse after meals. She says that she feels bloated all the time and often belches. She finds some relief with antacids, but the pain returns about 3 hours after each dose. She states that she began having these symptoms about 2 months ago and that they occur every other day. A UBT is positive for H. pylori. Her current medications include loratadine 10 mg/day and a daily multivitamin. She has a penicillin allergy.

45. Which treatment for H. pylori is best?
A. Levofloxacin 500 mg daily plus amoxicillin 1 g twice daily plus esomeprazole 40 mg twice daily for 10 days.
B. Amoxicillin 1 g twice daily plus clarithromycin 500 mg twice daily plus esomeprazole 40 mg twice daily for 14 days.
C. Bismuth subsalicylate 525 mg four times daily plus metronidazole 250 mg four times daily plus tetracycline 500 mg four times daily plus esomeprazole 40 mg once daily for 7 days.

D. Bismuth subsalicylate 525 mg four times daily plus metronidazole 250 mg four times daily plus tetracycline 500 mg four times daily plus omeprazole 40 mg twice daily for 14 days.

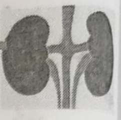
46. The patient presents for a follow-up 4 weeks after completing H. pylori treatment and asks her physician if the H. pylori infection has been cleared. Which laboratory assessment is best to confirm H. pylori eradication for this patient at this time?

A. Tissue culture.
B. UBT.
C. Rapid urease test.
D. Serum antibody test.

47. A 52 year old woman developed a portal hypertension secondary to cirrhosis for she has been taking appropriate doses of Furosemide and spironolactone. Today she comes to the outpatient department for regular follow up. What is the most likely clinical chemistry parameter to monitor this case?

A. Serum glucoses
C. Serum bicarbonate
B. Serum potassium
D. Serum creatine kinase

CHAPTER 3: RENAL DISORDERS



3.1. Estimating Renal Function

Introduction

- Estimating renal function is important for patients taking renally eliminated medications in order to maximize effectiveness while limiting toxicity. The glomerular filtration rate (GFR) is an effective indicator of renal function and normal values are approximately 130 mL/min/1.73 m^2 for men and 120 mL/min/1.73 m^2 for women. Numerous methods have been developed to estimate GFR and examples include the Cockcroft-Gault and the Modification of Diet in Renal Disease (MDRD) equations. When dosing medications based on renal function, either Cockcroft-Gault or MDRD are appropriate

Serume Creatinine

- *Creatinine* is an endogenous substance that is eliminated primarily by glomerular filtration and serves an important role in estimating RF.
- The range of serum creatinine (SCr) is approximately 0.6 to 1.2 mg/dL in normal, healthy adults.
- SCr is affected by *age*, *gender*, *race*, *diet*, *muscle mass*, and *certain drugs*; therefore, SCr is not used alone in predicting GFR.
  - ✓ High doses of trimethoprim, for example, may increase SCr values due to competition for active tubular secretion into the urine; however, renal function is unchanged.
  - ✓ Muscle mass is an important consideration when analyzing SCr values. Creatinine is a by-product of creatine metabolism and is influenced by the amount of muscle mass in a patient. Patients with low muscle mass would be expected to have lower SCr values. Low muscle mass can occur in elderly, cachectic (eg, AIDS patients), or individuals with limited muscle use (eg, spinal cord injury). Therefore, low muscle mass patients may have SCr values in the normal range but actually have renal insufficiency.

(1) Urinary Clearance of Creatinine

- GFR can be estimated via the combination of a timed urine collection and blood sampling of creatinine.
  - ✓ The most common time interval utilized is a 24-hour urine collection.
  - ✓ This practice has decreased due to the difficulty with accurate collection.

$$CrCl\ (ml/min) = \frac{Ucr\ x\ V}{Scr\ x\ t}$$

- Ucr = urine creatinine concentration, mg/dL
- V = volume of urine, mL
- Scr = serum creatinine concentration, mg/dL
- t = time of urine collection, minute
  - ❖ Note: time equals 1440 minutes for a 24-hour collection

(2) Cockcroft-Gault method[1]

$$CrCl\ (mL/mL) = \frac{[(140 - age) x \text{ ideal body weight (kg)}][(0.85 \text{ (for women)})]}{(72xSCr)}$$

- $Ideal\ body\ weight\ (men) = 50kg + (2.3\ x\ height\ in\ inches\ over\ 5\ feet)$
- $Ideal\ body\ weight\ (women) = 50kg + (2.3\ x\ height\ in\ inches\ over\ 5\ feet)$

(3) Modification of Diet in Renal Disease (MDRD) equation[2]

$$\text{GFR} = 186 \times (\text{Scr}^{-1.154}) \times (\text{age}^{-0.203}) \times 0.742 \text{ (if female)} \times 1.210 \text{ (if African American)}$$

(4) CKD Epidemiology Collaboration Creatinine Equation 2009 (CKD-EPI)[3]

$$\text{GFR} = 141 \text{ X } \min(\text{SCr/K},1)^{\text{alpha}} \text{ X } \max(\text{SCr/k}, 1)^{-1.209} \text{ X } 0.993^{\text{Age}} \text{ X Sex X Race X } 1.159 \text{ (if African American)}$$

- For females, the following values are used: Sex = 1.018; alpha = -0.329; kappa = 0.7
- For males, the following values are used: Sex= 1; alpha=-0.411; kappa = 0.9

Special Considerations

- The Cockcroft-Gault, MDRD and CKD-EPI equations are not validated in children and therefore should be used with caution when estimating renal function in pediatrics.
- The most common equation used to estimate renal function in children is the ***Schwartz*** equation[4].

$$\text{GFR (mL/min/1.73m}^2) = \frac{[\text{length (in cm)} \times \text{k}]}{\text{SCr}}$$

- Where k = 0.45 (age <1 year), 0.55 (age 1–13 years), 0.7 (adolescent male), or 0.55 (adolescent female)

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[1] Cockcroft DW, Gault H: **Prediction of creatinine clearance from serum creatinine.** *Nephron* 1976, **16**(1):31-41.

[2] Levey AS, Coresh J, Greene T, Stevens LA, Zhang Y, Hendriksen S, Kusek JW, Van Lente F: **Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate.** *Annals of internal medicine* 2006, **145**(4):247-254.

[3] Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro III AF, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T: **A new equation to estimate glomerular filtration rate.** *Annals of internal medicine* 2009, **150**(9):604-612.

[4] Schwartz GJ, Munoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, Furth SL: **New equations to estimate GFR in children with CKD.** *Journal of the American Society of Nephrology* 2009, **20**(3):629-637

Unstable Renal Function

- Equations such as Cockcroft-Gault and MDRD overestimate GFR during periods of renal function decline and underestimate GFR during periods of recovery.

> **Key Concepts** *SCr levels do not correlate well with GFR because there can be a lag in the rise and fall of SCr during* ***acute kidney injury****.*

- If a SCr doubles within 24 hours, the GFR is likely close to zero.
- Clinical judgment must be used to adjust medication dosages in patients with rapidly changing renal function.

3.2. Acute Kidney Injury (AKI)

Definition: AKI is a decrease in glomerular filtration rate (GFR),

- Generally occurring over hours to days, sometimes over weeks,
- Associated with an accumulation of waste products (urea and creatinine), disturbance in extracellular fluid volume and electrolyte and acid base homeostasis.
- Diagnostic criteria[1]
  - ✓Increase in SCr by at least 0.3 mg/dL within 48 hours or
  - ✓Increase in SCr by at least 1.5Xs baseline within the prior 7 days or
  - ✓Decrease in urine volume to less than 0.5 mL/kg/h for 6 hours
- Based on the ***amount of urine output*** AKI may be classified as:
  - ✓**Anuric**: if urine volume is <100 ml/day
  - ✓**Oliguric**: if urine volume is <400 ml/day
  - ✓**Non-oliguric**: if urine volume is ≥400 ml/day

Risk Factors

- Older age
- Higher baseline (SCr)
- Chronic kidney disease (CKD)
- Diabetes
- Chronic respiratory illness
- Underlying CVD
- Prior heart surgery
- Dehydration resulting in oliguria
- Acute infection
- Renal outflow obstruction
- Exposure to nephrotoxins.

Pathophysiology

(1) Prerenal AKI

- Prerenal AKI is the most common **(55%)** form of AKI. Represents a physiologic response to mild to moderate renal **hypoperfusion.** Prerenal AKI is rapidly reversible upon restoration of renal blood flow and glomerular ultrafiltration pressure. More severe hypoperfusion may lead to ischemic injury of renal parenchyma and intrinsic renal AKI

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[1] Bondi DS, Bridgeman MM, Burke JM, et al. **Updates in Therapeutics®: Pharmacotherapy Preparatory Review and Recertification Course**, 2021 ed. Lenexa, KS: American College of Clinical Pharmacy, 2021

- Major causes of prerenal AKI
  - i) **Hypovolemia**
    - ✓Hemorrhage, burns, dehydration
    - ✓GI fluid loss: vomiting, surgical drainage, diarrhea
    - ✓Renal fluid loss: diuretics, osmotic diuresis (DM), hypoaldestronism
    - ✓Sequestration in extravascular space: pancreatitis, peritonitis, trauma, burns, severe hypoalbuminemia
  - ii) **Low cardiac output**
    - ✓Diseases of myocardium, valves, and pericardium; arrhythmias; tamponade
    - ✓Other: pulmonary hypertension, massive pulmonary embolus
  - iii) **Systemic vasodilatation**: sepsis, anaphylaxis
  - iv) **Impairment of renal autoregulatory responses:** NSAIDS, ACE inhibition

(2) Intrinsic AKI

- Acute intrinsic AKI results from **damage to the kidney** itself
- Account for nearly **40%** of all AKI
  1. Renovascular obstruction (bilateral or unilateral)
  2. Disease of glomeruli or renal microvasculature
  3. Acute tubular necrosis (ATN): ischemia, toxins
  4. Interstitial nephritis (inflammation within the renal parenchyma)

(3) Post Renal AKI (Obstruction)

- Account for ~5% of AKI.
  1. ***Ureteric***: Calculi, blood clot, sloughed papillae, cancer, external compression (e.g., retroperitoneal fibrosis)
  2. ***Bladder neck***: Neurogenic bladder, prostatic hypertrophy, calculi, cancer, blood clot
  3. ***Urethra***: Stricture, congenital valve, phimosis

✍ **Signs and Symptoms of AKI**

- Peripheral edema, weight gain, nausea/vomiting/diarrhea/anorexia, mental status changes, fatigue, shortness of breath, pruritus, volume depletion (prerenal), colored/foaming urine, anuria alternating with polyuria (postrenal), colicky abdominal pain radiating from flank to groin (postrenal)

✍ **Diagnosis**

1. Decreased GFR
2. Elevated serum creatinine concentration (normal 0.6 to 1.2 mg/dL)
3. Elevated BUN concentration (normal 8 to 25 mg/dL)
4. **BUN: creatinine ratio** (elevated in prerenal AKI): >20:1 but <20:1 (intrinsic or postrenal AKI). This observation is due to the differences in

the renal handling of urea and creatinine. Recall that urea is reabsorbed with water, and under conditions of decreased renal perfusion both urea and water reabsorption are increased. Because creatinine is not reabsorbed, it is not affected by increased water reabsorption.

5. Urinalysis
   - ✓Red cell casts - vasculitis or glomerulonephritis
   - ✓Muddy brown granular casts and epithelial cell casts in a patient - acute tubular necrosis
6. Radiologic/imaging studies
   - ✓To assess urinary tract obstruction, kidney stones, renal cyst or mass
   - ✓Renal ultrasonography, plain film of the abdomen (KUB)

✍ Prevention and Treatment

- Desired Outcome
  - a) To prevent AKI
  - b) Avoid or minimize further renal insults that would worsen the existing injury or delay recovery, and
  - c) Provide supportive measures until kidney function returns
- General Approach to Treatment

Key Concepts *__Prerenal__ and __postrenal__ AKI can be reversed if the underlying problem is promptly identified and corrected, while treatment of __intrinsicrenal__ failure is more supportive in nature.*

✓ Supportive therapy such as fluid, electrolyte, and nutritional support, renal replacement therapy (RRT), and treatment of non-renal complications such as sepsis and gastrointestinal bleeding while regeneration of the renal epithelium occurs.

✓ In addition, prevention of adverse drug reactions by **discontinuing nephrotoxic drugs or adjustment of drug dosages**based on the patient's renal function is desired.

- **Pharmacologic Therapy**

1. **Loop Diuretics** (*furosemide, bumetanide, torsemide,* and *ethacrynic acid*)

✓ Diuretics currently have no role in preventing AKI progression or reducing mortality, but they can prevent complications, such as pulmonary edema.

✓ Loop diuretics are limited to instances of volume overload and edema. A usual starting dose of IV *furosemide* for the treatment of AKI is 40mg. For edema, IV furosemide (*80 to 120 mg*) is preferred because of its potency. If urine output does not increase to about 1mL/kg/hr, the dosage can be increased to a maximum of *160 to 200 mg* of furosemide or its equivalent A disadvantage of furosemide is its variable oral bioavailability and potential for ototoxicity with high serum concentrations attained with rapid, high-dose bolus infusions. Consequently, initial IV furosemide doses should not exceed 40 to 80 mg and should include close followup assessment of any response. Torsemide and bumetanide have more predictable oral BA and are more potent, 4:1 and 40:1, respectively, compared with furosemide. *Torsemide* has excellent oral BA and is unaffected by gut edema

- ✓ Closely monitor patient vital signs (wt, T⁰, BP, PR, and RR) several times per day. Diuresis should aim for a weight loss of *0.5 to 1.0 kg* per day. The patient's volume status should be assessed daily
- ✓ Other methods to improve diuresis can be initiated sequentially, like: shortening the dosage interval; adding HCT and switching to a continuous infusion loop diuretic.

2. **Thiazide diuretics**, when used as single agents, are generally not effective for fluid removal when creatinine clearance is less than 30 mL/minute.
3. **Potassium – sparing diuretics**, which inhibit sodium reabsorption in the distal nephron and collecting duct, are not sufficiently effective in removing fluid. In addition, they increase the risk of hyperkalemia in patients already at risk.

Key Concepts *Loop diuretics are the diuretics of choice for the management of volume overload in AkI*

4. **Dopamine:** *Low-dose* dopamine, in doses ranging from 0.5 to 3 mcg/kg per minute predominantly stimulates D1 receptors, leading to renal vascular vasodilation and increased renal blood flow

- **Nonpharmacologic Therapies**
  - ✓ Renal Replacement Therapy
    - ➢ RRT may be necessary in patients with AKI
      - ➭ To treat volume overload that is unresponsive to diuretics,
      - ➭ To minimize the accumulation of nitrogenous waste products, and
      - ➭ To correct electrolyte and acid-base abnormalities
    - ➢ Indications for RRT – **AEIOU**
      - ❖ **A**–*Acid*–base abnormalities: metabolic acidosis resulting from the accumulation of organic and inorganic acids
      - ❖ **E** – *Electrolyte imbalance*: hyperkalemia, hypermagnesemia
      - ❖ **I** – *Intoxications*: salicylates, lithium, methanol, ethylene glycol, theophylline, phenobarbital
      - ❖ **O** – *fluid Overload*: postoperative fluid gain/overload
      - ❖ **U** – *Uremia*: high catabolism of uremic toxins
  - ✓ Supportive Therapy
    - ➢ Supportive therapy in AKI includes adequate nutrition, correction of electrolyte and acid-base abnormalities (particularly hyperkalemia and metabolic acidosis), fluid management, and correction of any hematologic abnormalities.

- ➤ Finally, all drugs should be reviewed, and dosage adjustments made based on an estimate of the patient's glomerular filtration rate.

✍ Follow-up Evaluations

- In established AKI, daily measurements of **fluid intake and output** should be performed. **Vital signs** should be monitored at least daily or more often if the acuity of illness warrants it. **Electrolytes, BUN, Scr**, and a **CBC** should be considered routine and measured at least daily for hospitalized patients.

✍ Prevention of Acute Kidney Injury

- Avoidance: The best preventive measure for AKI, especially in individuals at high risk, is to avoid medications that are known to precipitate AKI.

3.3. Drug-Induced Kidney Disease (DIKD)

✍ Principles for Prevention of DIKD

- The primary principle for prevention of DIKD is to avoid the use of nephrotoxic agents for patients at increased risk for toxicity. Therefore, an awareness of potentially nephrotoxic drugs and knowledge of risk factors that increase kidney vulnerability are essential. Exposure to these drugs often cannot be avoided; so, several interventions have been proposed to reduce the potential for the development of nephrotoxicity, for example, adjustment of medication dosage regimens based on accurate estimates of kidney function, and careful and adequate hydration to establish high urine flow rates.

✍ Tubular Epithelial Cell Damage

- Drugs that lead to ***renal tubular epithelial cell (RTEC) damage*** typically do so via direct cellular toxicity or ischemia. Damage is most often localized in the proximal and distal tubular epithelia and is termed "ATN" when cellular degeneration and sloughing from proximal and distal tubular basement membranes are observed.
- **Acute Tubular Injury/Necrosis:** the primary agents associated with this type of injury are aminoglycosides, radiocontrast media, cisplatin, amphotericin B, foscarnet, and osmotically active agents such as immunoglobulins, dextrans, hydroxyethyl starch, and mannitol

  I) Aminoglycoside Nephrotoxicity

  - ✓ Aminoglycoside antibiotic–associated nephrotoxicity may occur in between 10 and 25% of patients receiving a therapeutic course. Critically ill patients appear to have a higher risk for nephrotoxicity with rates as high as 58%.
  - ✓ Clinical evidence of aminoglycoside-associated nephrotoxicity is typically seen within ***5 to 7 days*** after initiation of therapy and manifests as a gradual progressive rise in Scr and BUN and decrease in creatinine clearance. Full recovery of kidney function is common if aminoglycoside therapy is discontinued immediately upon discovering signs of toxicity.

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